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EXAMINER

UNGAR, S

ART UNIT

PAPER NUMBER

1642

13

DATE MAILED:

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/125,751

Applicant(s)

Fodstad et al

Examiner

Ungar

Group Art Unit

1642



☒ Responsive to communication(s) filed on Jan 3, 2000

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1, 3, 6-8, 13, and 14 is/are pending in the application.

Of the above, claim(s) 13 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1, 3, 6-8, and 14 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 2, 4, 3, 9

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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1. The Election filed January 3, 2000 (Paper No. 11) in response to the Office Action of November 9 1999 (Paper No. 7) is acknowledged and has been entered. Claim 1 has been amended, claims 4, 5 and 9-12 have been canceled, claim 14 has been added and claim 13 has been withdrawn from further consideration by the examiner under 37 CAR 1.142(b) as being drawn to a non-elected invention.s. Claims 1, 3, 6-8 and 14 are currently under prosecution

2. It is noted that the numbering of the newly added claim is not in accordance with 37 CAR 1.126. The original numbering of the claims must be preserved throughout the prosecution. When claims are added, except when presented in accordance with 37 CAR * 1.121(b), they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Misnumbered claim 13 has been renumbered claim 14.

Specification

3. The use of the trademarks such as ISOLEX 50 and ISOLEX 300 disclosed on page 5, line 4, of the specification has been noted in this application. They should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Each letter of the trademarks must be capitalized. See MPEP 608.01(V) and Appendix I.

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4. The specification contains a number of spelling errors, for example, toxicity on p. 5, line 29, immunotixins on the last line of the abstract, with on p. 3, line 10. Further, in the specification on p. 3, line 32, it is not understood what "damage to the normal cells can" means and there appears to be an inadvertent typographical error.

Examiner has made an effort to identify these informalities but applicant must carefully review the specification to identify and indicate where such informalities occur. Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

6. Claims 1, 3 and 6-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method to kill breast cancer or other carcinoma cells comprising purging tumor cells which express both EGP2 and MUC-1 from a cell population comprising nucleated cells in peripheral blood *ex vivo*, does not reasonably provide enablement for said method *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

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The claims are drawn to a method to kill breast cancer cells or other carcinoma cells expressing the same target antigens in a cell population comprising nucleated cells in peripheral blood, or CD-34+ cells selected from the above nucleated cells or other immature/early progenitor cells from blood containing multipotent stem cells comprising exposing the cell population to a combination of two immunotoxins (ITs) wherein each is composed of an antibody and toxin wherein the antibodies are directed to epitopes on the antigen EGP2 and MUC-1. This includes exposure both *in vitro* and *in vivo*. The specification teaches that the present invention relates to purging of harvested stem cell populations in cases of solid tumors in which method the cell population is exposed to two or more antibodies conjugated to bacterial toxins wherein the antibodies are directed to target cell-associated antigens (p. 4, lines 7-11) and that due to the high specific activity of the disclosed immunotoxins *in vitro* **it seems possible to** (emphasis added) administer the mixture for *in vivo* treatment of patients suffering from different types of carcinoma (p. 12, lines 31-33). An important problem in using immunotoxins *in vivo* is that their half lives often are very short, i.e. the immunotoxins are broken down and removed from blood before the concentration is adequately high (p. 13, lines 9-12). One cannot extrapolate the teaching of the specification to the scope of the claims because it was well known in the art at the time the invention was made that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening

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began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). It is clear that the unpredictability of the art is well known to Applicant as demonstrated by the statement in the specification that "it seems possible to administer the mixture for in vivo treatment of patients suffering from different types of carcinoma". Because of the known unpredictability of the art, in the absence of experimental *in vivo* evidence, no one of skill in the art would accept the assertion that, based on the high specific activity of the disclosed immunotoxins *in vitro*, that administration of the mixture could be used for *in vivo* treatment of patients suffering from different types of carcinoma. The specification does not provide teachings to establish effective dosages or methods of administration of antibodies specific for the two epitopes and no working examples are provided which would provide sufficient guidance to allow one skilled in the art to practice the above embodiments of the invention with a reasonable expectation of success. Clearly, an anti-tumor cell agent must accomplish several tasks to be effective. It must be delivered to the site of the target cells to be killed, interact at the proper site of action and must do so at a sufficient concentration and for a sufficient period of time. In addition the target cell must not have an alternate means of survival despite action at the proper site. *In vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the assays, the anti-tumor cell agent is in contact with cells during the entire exposure period. This is not the case *in vivo*, where exposure at the target site may be delayed or inadequate. In addition variables such as biological stability, half-life or clearance from the blood are

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important parameters in achieving successful therapy. The conjugate may be inactivated *in vivo* before producing a sufficient effect, for example, by proteolytic degradation, immunological activation or due to an inherently short half life of the antibody and the *in vitro* tests of record do not sufficiently duplicate the conditions which occur *in vivo*. In addition, the antibody may not otherwise reach the target because it may be absorbed by fluids, cells and tissues where it has no effect, and a large enough local concentration may not be established.

Further, the claims are drawn to the method, *in vivo* wherein CD-34+ cells or other immature/early progenitor cells are selected from the nucleated cells in peripheral blood. There is no teaching of how to accomplish this particular limitation *in vivo* and although methods for enriching populations of hematopoietic cells are well known *ex-vivo*, neither the art of record nor the specification provides any guidance on how to accomplish this critical step *in vivo*. Thus the specification clearly does not teach how to make the invention as claimed. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success.

7. The specification is objected to and claim 3 is rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure, because the specification

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does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from a written description (e.g. sequenced); or (3) deposited.

The claim is drawn to monoclonal antibodies MOC31 and BM7 conjugated to a toxin.

It is unclear if cell lines which produce antibodies having the exact structural and chemical identity of MOC31 and BM7 are known and publicly available, or can be reproducibly isolated without undue experimentation. Clearly, without access to a hybridoma cell line producing monoclonal antibody MOC31 and a hybridoma cell line producing monoclonal antibody BM7, it would not be possible to practice the claimed invention. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical

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characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species, MOC31 and BM7. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809.

Applicant has not disclosed the deposit of hybridoma cell lines that would reproduce the antibody species, MOC31 and BM7.

If a deposit has been made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

In addition to the conditions under the Budapest Treaty, applicant is required to satisfy that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications. Applicant's provision of these assurances would obviate this objection/rejection.

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Affidavits and declarations, such as those under 37 C.F.R. § 1.131 and 37 C.F.R. § 1.132, filed during prosecution of the parent application do not automatically become a part of this application. Where it is desired to rely on an earlier filed affidavit, the applicant should make the remarks of record in the later application and include a copy of the original affidavit filed in the parent application

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of the deposit.

If the original deposit is made after the effective filing date of an application for patent, the applicant should promptly submit a verified statement from a person in a position to corroborate the fact, and should state, that the biological material which is deposited is a biological material specifically identified in the application as filed, except if the person is an attorney or agent registered to practice before the Office, in which the case the statement need not be verified. See MPEP 1.804(b).

8. Claims 1, 3, 6-8 and 14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) Claims 1, 3, 6-8 and 14 are indefinite because claim 1 recites "other immature/early progenitor cells" because the claim(s) include(s) elements not actually disclosed (those encompassed by "other immature/early progenitor cells"), thereby rendering the scope of the claim(s) unascertainable. See MPEP § 2173.05(d).

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(B) Claims 1, 3, 6-8 and 14 are indefinite because claim 1 recites the phrase “characterized in”. The phrase is confusing because it is not clear that the characterization is limited to the exposure of the cell population to the immunotoxin or to the other limitations claimed. The rejection can be obviated by amending the claims to delete the phrase “characterized in” and substituting the term “wherein”.

(C) Claims 1, 3, 6-8 and 14 are indefinite because claim 1 recites the phrase “fragments of antibodies and toxin”. The claims are confusing because it is not clear whether the fragments of antibodies claimed are those that bind to antigen or whether the toxin fragments claimed are active fragments. The rejection can be obviated by amending claim 1, for example, to read antigen binding antibody fragments and active toxin fragments.

(D) Claims 1, 3, 6-8 and 14 are indefinite because claim 1 recites the phrase “by the genes MUC1”. The claims are indefinite because only one gene the MUC1 gene is recited. The rejection can be obviated by amending the claim to read “expressed by the MUC1 gene”.

(E) Claim 3 is indefinite in the recitation of the phrase “or fragments thereof” for the reasons set forth above. The rejection can be obviated by amending the claim to read “antigen binding fragments thereof”.

(F) Claims 6, 7 and 13 is indefinite in the recitation of the term “administered” because there is no antecedent basis for the term in claim 1 from which it depends. The rejection can be obviated by amending claims 6 and 13 to recite, for example, “wherein said exposure consists of administering”.

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(G) Claim 3 is indefinite in the recitation of antibodies MOC31 and BM7 as the sole means of identifying the claimed antibodies. The use of laboratory designations only to identify a particular antibody/cell line renders the claims indefinite because different laboratories may use the same laboratory designations to define completely distinct hybridomas and antibodies. Amendment of the claims to include the depository accession number of the mAb or hybridoma is required, because deposit accession numbers are unique identifiers which unambiguously define a given hybridoma and/or monoclonal antibody.

(H) Claims 1, 3, 6-8 and 14 are confusing because it is not clear whether the method is drawn to killing CD-34+ cells selected from the above nucleated cells or other immature/early progenitor cells as well as killing breast cancer cells or other carcinoma cells or whether the method is drawn to killing breast cancer cells or other carcinoma cells in a cells population comprising nucleated cells in peripheral blood or in a population of CD-34+ enriched cells or other immature/early progenitor cells. It appears that the claim is meant to be a markush claim but that it is written in improper markush format. The Office recommends the use of the phrase "selected from the group consisting of..." with the use of the conjunction "and" rather than "or" in listing the species. MPEP 2173.05(h). The rejection can be obviated by amending the claim to delete the comma (,) after peripheral blood on line 3 of the claim and by using the proper markush format to identify the species of cell populations where breast cancer or other carcinoma cells are to be killed.

Claim Rejections - 35 USC § 103

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9. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

10. Claims 1 and 14 are rejected under 35 U.S.C. § 103 as being unpatentable over Lemoli et al (Bone Marrow Transplantation, 1994, 13:465-471, IDS item) in view of Brugger et al (Blood, 1994, 83:636-640), Parry et al (J. Cell Science, 1992, 101:191-199), Bjorn et al (Cancer Res., 1986, 46:3262-3267, IDS item) and US Patent No. 5,185,254.

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The claims are drawn to a method to kill breast cancer cells or other carcinoma cells expressing the same target antigens in a cell population comprising nucleated cells in peripheral blood, or CD-34+ cells selected from the above nucleated cells or other immature/early progenitor cells from blood containing multipotent stem cells comprising exposing the cell population to a combination of two immunotoxins (ITs) wherein each is composed of an antibody and toxin wherein the antibodies are directed to epitopes on the antigen EGP2 and MUC-1, wherein the immunotoxins are administered *ex vivo*.

Lemoli et al teach a successful *ex vivo* method, in a cell population of CD-34+ cells extracted from bone marrow, of purging (killing) neoplastic lymphoma cells comprising exposing the cell population to two immunotoxins specific for two different antigens expressed on the lymphoma cells (see abstract and p. 469, col 2). Lemoli et al further teach that highly enriched populations of hematopoietic CD34+ progenitors have been used for autologous hematopoietic reconstitution in humans and that if CD34+ cells could be purified without tumor cells, then this technique may provide an alternative approach to the methods presently used for elimination of contaminating cancer cells from autologous grafts.

Lemoli et al teach as set forth above but do not teach a method wherein the CD-34+ cells are in peripheral blood before extraction or teach a method of killing breast cancer cells wherein the immunotoxins are directed against antigen EGP2 or MUC-1.

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Bjorn et al (Cancer Res., 1986, 46:3262-3267, IDS item) teaches that Breast cancer is a leading cause of death among women and that monoclonal antibodies conjugated to PE kill breast cancer cells *in vitro* (see abstract).

Brugger et al teach that peripheral blood progenitor cells are increasingly used for autografting after high-dose chemotherapy (see abstract) and that a high proportion of breast cancer patients have circulating tumor cells and that there is a substantial risk of concomitant tumor cell recruitment upon mobilization of PBPCs, particularly in stage IV breast cancer patients (see abstract).

Parry teaches that MUC-1 is a major mucin glycoprotein expressed on the surface of mammary epithelial cells and is an antigen found on many breast tumor cells where it is over expressed and teaches monoclonal antibodies to MUC-1 (see abstract).

US Patent No. 5,185,254 teaches Mab GA733 and CO17-1A which bind to an antigen expressed by the GA733-2 gene (col 4, lines 20-25) and further teaches that Mab GA733 binds to breast tumor carcinoma and to varying degrees to normal epithelial tissues (col 1, lines 20-30).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute peripheral blood stem cells isolated from breast cancer patients as taught in Brugger et al for the CD-34+ cells extracted from bone marrow in the method of Lemoli et al because Lemoli et al teach that CD34+ cells can be successfully purified of tumor cells *ex vivo* and can be used for autologous hematopoietic reconstitution in humans and because Brugger et al teach that peripheral blood stem cells are increasingly used for the same purpose, that is

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for autografting after high-dose chemotherapy and because Brugger et al specifically teach that there is a substantial risk of mobilization of concomitant tumor cells upon mobilization of the peripheral blood stem cells, particularly in breast cancer patients. Further, it would have been *prima facie* obvious to substitute the antibodies taught in Parry et al against MUC-1 and US Patent No. 5,185,254 against GA-733.2 for the antibodies of Lemoli et al and conjugate them to toxins in the method of Lemoli et al because the antibodies are preferentially expressed on epithelial cells and are taught to be specific for antigens expressed on breast tumor cells and it would be expected that the antibodies would successfully differentiate between tumor cells expressing the antigens and nucleated cells from peripheral blood. One of ordinary skill in the art would have been motivated to substitute peripheral blood stem cells isolated from breast cancer patients as taught in Brugger et al for the CD-34+ cells extracted from bone marrow in the method of Lemoli et al and to further substitute the antibodies taught in Parry et al against MUC-1 and US Patent No. 5,185,254 against GA-733.2 for the antibodies of Lemoli et al and conjugate them to toxins in the method of Lemoli et al in order to remove contaminating tumor cells from stem cells to be used in autologous hematopoietic grafts. Finally one of ordinary skill in the art would have expected to successfully kill the breast cancer cells because Bjorn et al teaches that monoclonal antibodies that bind to breast tumor cells and are conjugated to PE kill breast cancer cells in *vitro*.

9. No claims allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is

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(703) 305-2181. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached at (703) 308-3995. The fax phone number for this Art Unit is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.

A handwritten signature in black ink, appearing to read "Susan Ungar", with a stylized flourish at the end.

Susan Ungar
Patent Examiner
April 3, 2000